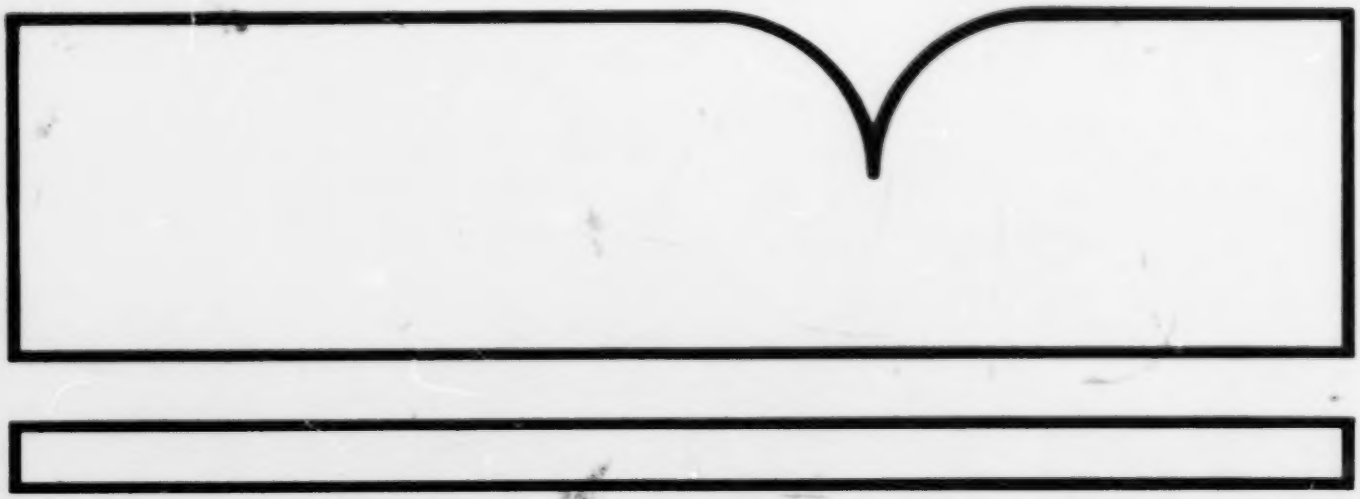
PB81-192122

Motor Activity: A Survey of Methods with Potential Use in Toxicity Testing

(U.S.) Health Effects Research Lab.
Research Triangle Park, NC

1979



U.S. Department of Commerce
National Technical Information Service
NTIS

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

MS-80-060

1. REPORT NO.	2.	3
EPA-600/J-79-121	JOURNAL ARTICLE	PB81-192122

4. TITLE AND SUBTITLE	5. REPORT DATE
Motor Activity: A Survey of Methods with Potential Use in Toxicity Testing	April 1981
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
L.W. Reiter and R.C. MacPhail	
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
Neurotoxicology Division Health Effects Research Lab US Environmental Protection Agency Research Triangle Park, NC 27711	1LA629
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Office of Research and Development (RTP,NC) Health Effects Research Lab Research Triangle Park, NC 27711	14. SPONSORING AGENCY CODE EPA-600/11

15. SUPPLEMENTARY NOTES

Published In: Neurobehavioral Toxicology 1(1), 53-66, 1979

16. ABSTRACT

Activity Measurements are expected to have widespread use in toxicity testing. The multifaceted nature of motor activity will directly influence the selection of a measurement technique since the relative contribution of various motor acts to any particular measurement will depend upon the detection method. Because of the apparatus-dependent nature of motor activity measurements, it is recommended that consideration be given to how accurately the various devices measure locomotive activity. In the preasent paper, two types of body movement will be considered as locomotor activity: ambulation (horizontally directed movement) and rearing (vertically directed movement). Discussion focuses on the various methods currently used to record motor activity, the various components of motor activity which are likely to be recorded, and the advantages and disadvantages of these techniques for the measurement of locomotor activity. Finally, consideration is given to studies which have compared treatment effects on motor activity derived from two or more measurement techniques.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
motor activity toxicity testing measurement techniques		06T

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
RELEASE TO PUBLIC	UNCLASSIFIED	
	20. SECURITY CLASS *(This page)*	22. PRICE
	UNCLASSIFIED	

EPA Form 2220-1 (9-73)

PRODUCT OF:
NATIONAL TECHNICAL INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

Test Methods for Definition of Effects of Toxic Substances on Behavior and Neuromotor Function
Neurobehavioral Toxicology, Vol. 1, Suppl. 1, pp. 53–66. ANKHO International Inc., 1979.

MS-80-060

EPA-600/J-79-121
Journal Article

Motor Activity: A Survey of Methods with Potential Use in Toxicity Testing

LAWRENCE W. REITER AND ROBERT C. MACPHAIL

Neurotoxicology Division, Health Effects Research Laboratory, U.S. Environmental Protection Agency
Research Triangle Park, NC 27711

REITER, L. W. AND R. C. MACPHAIL. *Motor activity: A survey of methods with potential use in toxicity testing.* NEUROBEHAV. TOXICOL. 1: Suppl. 1, 53–66, 1979.—Activity measurements are expected to have widespread use in toxicity testing. The multifaceted nature of motor activity will directly influence the selection of a measurement technique since the relative contribution of various motor acts to any particular measurement will depend upon the detection method. Because of the apparatus-dependent nature of motor activity measurements, it is recommended that consideration be given to how accurately the various devices measure locomotor activity. In the present paper, two types of body movement will be considered as locomotor activity: ambulation (horizontally directed movement) and rearing (vertically directed movement). Discussion focuses on the various methods currently used to record motor activity, the various components of motor activity which are likely to be recorded, and the advantages and disadvantages of these techniques for the measurement of locomotor activity. Finally, consideration is given to studies which have compared treatment effects on motor activity derived from two or more measurement techniques.

Motor activity Toxicity testing Measurement technique

THE Toxic Substances Control Act specifically includes behavioral disorders as a health effect for which standard test data are to be developed. Behavioral testing will be used to evaluate both new substances and substances currently in commerce. Although it is likely that the strategy for these two test situations may be quite different, the actual test systems employed may overlap. New substances need to be tested for their neurotoxic properties. In this case, a series of behavioral tests is needed which will provide a reliable forecast of neurotoxicity. The greatest concern here is that a neurotoxicant not go undetected. On the other hand, testing of substances currently in use should focus on more clearly defining the neurotoxicity and should, therefore, be concerned with characterizing the types of behavioral changes associated with exposure along with the factors which influence these changes. Nevertheless, in both situations, there is a need for behavioral test systems which are reliable, sensitive and cost-effective.

It is very likely that motor activity will be widely used in evaluating toxic substances, see [44, 79, 88]. In the present paper, discussion of locomotor activity will focus on two types of body movement: ambulation (horizontal movement) and rearing (vertical movement). Next we will consider measurement techniques that are used with rodents including both observational and automated techniques. Consideration will be given to the behavioral components that contribute to different measures of activity including the fidelity with which the devices measure locomotor activity. Finally, we will examine the issue of cross reliability by reviewing experiments which compared two or more measures of motor activity.

GENERAL MOTOR ACTIVITY VS LOCOMOTOR ACTIVITY

Motor activity is not a unitary class of behavior. The terms "general motor activity" and "spontaneous motor activity" refer to the numerous motor acts, occurring either alone or in combination, which constitute an animal's behavioral repertoire. Quantitation of the general activity level of a rodent requires measurement of the total frequency of acts, such as walking, rearing, sniffing, grooming, etc. Because of the heterogeneous nature of general activity, it is doubtful that a single measure could ever be developed. Skinner [105], recognizing this point, concluded that "no attempt is made to distinguish between the various forms that the activity may take. Since each form should have its own units, a quantitative measure of activity as a whole is practically impossible."

Many investigators have utilized observational techniques to quantitate general activity. Draper [24], for example, developed an extensive list of descriptive behavioral units which he used to record the home-cage activity of rats (see Table 1). These behavioral units were divided into three categories: ambulatory, non-ambulatory and inactivity. The extensive (albeit incomplete) nature of this list should be cause for concern when one considers that a toxicant could differentially affect the various components of an animal's general activity. Norton [70], for example, used time-lapse photography to examine the effects of amphetamine on 15 components of general activity in rats. Her results demonstrated (see Table 2) that amphetamine produced a differential effect on the frequency of occurrence of various motor

TABLE 1

BEHAVIORAL COMPONENTS OF HOME CAGE ACTIVITY OF RATS

Ambulatory Movements	
(a) Vigorous	
(1) Chase tail	–Rapid circular movement with tail in or near mouth
(2) Climb	–Movement across sides or roof of cage, all four feet off floor
(3) Jump	–Quick upward jump, all feet leave floor
(4) Roll over	–Turn onto back or completely over
(5) Run	–Rapid movement across floor of cage
(b) Non-Vigorous	
(1) Circle	–Slow circular shifting of position similar to that seen in dogs or cats prior to sleep
(2) Stand on cage	–Front feet raised off floor, placed on sides of cage
(3) Rear	–Front feet raised off floor or held close to body
(4) Stretch	–Back arched, front, rear legs extended
(5) Walk	–Any leg movement that moves animal slowly across floor, roof or sides of cage
Inactivity	
(a) "Relaxed" position	
(1) Head under	–Head tucked under front feet, forehead on floor
(2) Side	–Head on side on floor, body curled around
(b) "Alert" position	
(1) Stomach	–Animal on stomach, head erect, immobile
(2) Stand still	–Animal stands, body off floor, immobile
Non-Ambulatory Movements*	
(a) Groom	
(1) Bite coat	–Quick bite into fur
(2) Lick coat	–Smoothing fur with tongue
(3) Genitals	–Bite or lick genital area
(4) Nails	–Chewing feet or nails
(5) Wash face	–Stroking whiskers and/or face with one or both front feet
(6) Scratch	–Quick scratch of ear or coat with hind leg
(7) Chew tail	–
(b) "Scanning" movements	
(1) Sniff	–Nose wrinkles, audible sniff
(2) Turn head	–Horizontal or vertical head movement
(c) Displaced Activity	
(1) Chew cage	–Chew bars of cage
(2) Chew chain	–Chew chain holding bottle on cage
(d) Miscellaneous movements	
(1) Shake	–Quick shake of entire body
(2) Twitch	–Small movement of portion of body
(3) Sneeze	–
(4) Yawn	–

*Ambulatory and non-ambulatory movements are not mutually exclusive.
From: Draper (Behaviour **28**: 280–293, 1967)

components of activity. Whereas behaviors such as walking and rearing increased following amphetamine, others such as grooming and sitting decreased, and still others including turning, looking (stationary head orientation) and pawing showed no consistent alteration. Since psychoactive chemicals may differentially alter the frequencies of the motor items comprising general activity, any attempt to quantitate this activity, short of recording all motor components, may be "practically impossible". Regardless of the technique which is employed to measure activity, it is essential to understand which components of motor activity contribute to that measure.

TABLE 2

TOTAL OCCURRENCES OF BEHAVIOR ACTS IN 15 MIN

	8 Saline Control Rats per Group			8 Amphetamine Rats per Group (mg/kg)		
				0.25	0.5	1.0
	A	B	C	A	B	C
Acts Increased by Amphetamine						
Bobbing	211	222	206	293*	356*	248
Rearing	1554	1785	1932	1935*	1848	2906*
Turning	153	167	117	273*	344*	365*
Walking	517	417	384	745*	926*	1139*
Acts Decreased by Amphetamine						
Eating	239	116	210	46*	28*	0*
Grooming	148	139	141	70*	19*	4*
Patting	87	85	110	44*	21*	14*
Scratching	26	39	45	18	6*	7*
Sitting	893	684	786	461*	423*	138*
Smelling	2358	2368	2377	2314	1756*	1719*
Standing	4097	1473	3936	3833*	3771*	2658*
Washing Face	219	265	338	205	159*	36*
Acts Not Consistently Altered by Amphetamine						
Head Turning	872	904	824	993	972	902
Looking	1425	1265	1189	1416	1491*	747
Pawing	60	60	37	45	45	31

*Significant difference ($p \leq 0.05$) using t-test to compare 8 control rats with 8 amphetamine-treated rats observed during the same 15 min

From: Norton (Physiol. Behav. **11**: 181–186, 1973)

The multifaceted nature of motor activity impacts directly on the use of automated measurement techniques, since the relative contribution of various motor acts to any particular measurement of activity will depend upon the detection method. In this regard, Draper [24] cautioned that the use of automated techniques has, on occasion, caused confusion since the concept of activity has become apparatus bound, and hence provides no common unit for purposes of comparison.

One major aspect of general motor activity is locomotor activity which, in the strictest sense, is defined as movement from one place to another. This movement can be either horizontally directed ambulation, including walking and running, or vertically directed including rearing, climbing, and jumping. In this discussion locomotor activity will include these two types of movement although in most experimental situations vertically directed movement is restricted to rearing.

METHODS USED TO MEASURE MOTOR ACTIVITY

A. OBSERVATIONAL TECHNIQUES

To some extent, the direct observation of behavior should always be included in toxicity testing. There will always be a need for information on the animal's general condition. The initial use of direct observation may provide important information on the toxicological properties of a compound which in turn increases the likelihood of detecting behavioral changes that may otherwise go unnoticed [39]. Toman and Everett [126], for example, noted the characteristic hunchback posture of reserpine-treated rats which would have gone undetected by most automated activity monitoring devices. The important question here, however, concerns the degree to which observational techniques may be employed in critically evaluating toxicant-induced changes in behavior.

Observational techniques employ either quantitative or qualitative measurements (Table 3). With the quantitative approach, the frequency, duration and/or sequencing of various motor components of behavior are measured. Norton, Mullenix and Culver [72], for example, have used this technique to evaluate activity in rats that had sustained brain damage from x-irradiation, carbon monoxide and pallidal lesions. In their study, the frequency and duration of 15 motor acts and the sequencing of pairs of acts were determined. An intriguing finding was that disruptions of motor sequencing were directly correlated with increases in photocell-activity counts, indicating that the increased activity measured in a photocell cage reflected a loss of the normal sequencing of behavior.

The qualitative approach is used to collect data on the presence or absence of certain components of activity. This approach is best exemplified by check lists and rating scales which have been developed by various investigators [45,135]. Use of these qualitative observational techniques has been limited primarily to the study of the acute effects of psychoactive drugs. They are well suited for identifying

TABLE 3

OBSERVATIONAL TECHNIQUES

A. Type of Measurement

1. Quantitative – measures the frequency, duration, and/or sequencing of various motor components of behavior

   Norton (1973), Norton et al. (1976)
   Premack (1965)

2. Qualitative – measures the presence or absence of certain motor components of behavior, i.e. check lists or rating scales

   Weismann et al. (1966)
   Irwin (1968)

B. Type of Environment

1. Home cage

   Draper (1967)

2. Novel environment, i.e. open field, Y-mazes, etc.

   Hall (1934)
   See Reviews by Walsh and Cummins (1976) and Archer (1973)

gross changes in behavior such as tremors, ataxia, or stereotypies.

However, the use of observational techniques to detect subtle changes in behavior has three major limitations: (1) The techniques require considerable commitments of time and manpower for the data-collection process. Depending on the precision to which general activity is characterized, more than one observer may be required [103]. (2) Because of possible subjective influences on the data-collection process, a considerable degree of technical competency is required to insure reliability. The problem of interobserver reliability is especially important when interlaboratory comparisons are to be made. In this case, a minimal requirement is that strict, objective criteria are used to identify the various motor components of activity. (3) When direct observation of behavior is employed, subject-observer interaction may be an important consideration. The mere presence of the observer may modify the animal's behavior. For example, McCall *et al.* [64] demonstrated that the distribution of a rat's activity in an open field tended to concentrate on the side closest to the observer.

The use of video-tape recordings or time-lapse photography has increased considerably in observational analysis. In most instances, this has minimized the problem of subject-observer interaction and also has provided a permanent record of behavior which can be used for standardizing observations, both within and between laboratories. Recent advances in computer-automated pattern-recognition techniques have also been applied to behavioral analysis [73]. Since rigidly defined criteria are required for computer-automated identification of the various motor components of behavior, this has alleviated somewhat the problems of subjectivity and labor-intensive data collection discussed above.

Experiments using observational techniques to measure motor activity frequently remove the animal from the home cage and observe its behavior in a novel environment. The complexity of this environment has ranged from a flat surface to a simple cubicle (resembling the home cage) to complex mazes consisting of interconnecting alleys.

TABLE 4

CLASSIFICATION OF OPEN-FIELD-DEPENDENT PARAMETERS

I. Behavior

A. Whole or Major Body Movement

1. Type of movement

   a. Distance covered per unit time
   b. Time spent in ambulation
   c. Rearing frequency
   d. Escape attempts
   e. Latency (usually time taken to leave start area)
   f. Time spent without movement

2. Locations

   a. Field area visited (inner or peripheral areas, corners, etc.)
   b. Affiliation (distance from partner subject)
   c. Stimulus interaction (e.g., distance from stimulus object)

B. Part Body Movement

1. Manipulation of objects
2. Sniffing
3. Scratching
4. Digging
5. Teeth chattering
6. Grooming
7. Vocalization
8. Visual exploration

II. Autonomic Nervous System

A. Defecation
B. Digestive Transit Time
C. Urination
D. Heart Rate and Rhythm
E. Respiratory Rate

III. Adrenal Activity

A. Adrenal Ascorbic Acid
B. Serum Corticosteroids

IV. Electrophysiology

A. Hippocampal Theta Activity
B. Electromyogram Activity

From: Walsh and Cummins (Psychol. Bull. 83: 482–504, 1976). Copyright (1976) by the American Psychological Association. Reprinted by permission.

The most extensively employed test environment has been the open field (for review see [3,132]). Much of its popularity is almost certainly due to the simplicity of the apparatus. With few exceptions, an open field is defined as an arena that is considerably larger than the cage used to house the animal [91].

Table 4, taken from a review by Walsh and Cummins [132], lists the dependent variables which have been measured in the open field. The most widely recorded classes of behavior include ambulation (often distinguished on the basis of whether ambulation occurs in the inner or peripheral

areas of the arena), frequency of rearing and grooming, and latency to first crossover. Typically, the floor of the open field is marked off into a grid arrangement and ambulation is measured by the number of times an animal enters a new square (crossovers).

The simplicity of design and ease of use of the open field almost certainly insure its continued use in behavioral testing. However, the numerous factors, both environmental and organismic, which influence open field measurements (e.g., size, illumination, species, sex and experience) require that investigators extensively report the methods employed. Surprisingly little consideration has been given toward standardization of the open field. Walsh and Cummins ([132], p. 493) summarized the problem as follows:

"Almost every physical characteristic of the apparatus, its surroundings and every procedural step have been widely varied, so that although standardization may have been established within individual laboratories, there is a disturbing lack of conformity in procedure and results within the literature as a whole.

In fact, it is hard to think of any facet which has not been modified. This difficulty of standardization is compounded by the extreme rarity of reports which cite details of more than a small proportion of relevant procedural variables."

Observational techniques have also been used with rodents tested in a complex environment such as a Y-maze. The maze consists of three alleys which join to form a Y. With this apparatus Steinberg and coworkers [92, 93, 111] have evaluated the effects of psychoactive drugs and past experience on ambulation (alley entrances) and rearing.

B. AUTOMATED TECHNIQUES

A variety of techniques have been employed to automatically record motor activity in rodents, the major classes of which are listed in Table 5. Photocell devices, field detectors and touch plates all provide direct measurements of activity because they measure the movement of the animal. The mechanical devices, on the other hand, provide an indirect measurement because they detect movement of the cage.

TABLE 5

AUTOMATED TECHNIQUES

A. Photocell Measurements
   1. Simple environment
      a. Horizontal (Siegel, 1946; Dews, 1953)
      b. Vertical (Schnitzer and Ross, 1960)
   2. Complex environment
      Norton et al. (1975)
      Ljungberg and Ungerstedt (1977)

B. Mechanical Measurements
   1. Stabilimeter
      a. Jiggle cage
         Richter (1927)
      b. Tilt cage
         Bousfield and Mote (1946)
         Campbell et al. (1961)
      c. Force platform
         Denenberg et al. (1975)
         Segal and Mandell (1974)
   2. Wheels
      Stewart (1898)
      Skinner (1933)

C. Field Detectors
   1. Ultrasonic
      Peacock and Williams (1962)
   2. Capacitance of a resonant circuit
      Svensson and Thieme (1969)

D. Touch plates (proximity counter)
   Silbergeld and Goldberg (1973)

1. Photocell Devices

Photocell devices provide direct, relatively unambiguous measures of motor activity in which beams of light traverse a cage and impinge on photoreceptors. Any movement of an animal which interrupts a beam is recorded as an activity count; in most cases, the process of detection provides no feedback to the animal which may affect subsequent activity. Photocell chambers are stationary and therefore are free of momentum (carry-over) effects. The use of an infrared light source allows recording during the nocturnal period without detection by the animal. The greatest limitation of this technique is the possible contamination of the data with nonlocomotor activities (e.g., movements of the head and paws) when these occur immediately in front of a photobeam.

Photocell devices may be categorized primarily in terms of the complexity of the test environment and, secondarily, in terms of the number and orientation of the photobeams.

a. Simple test environments are typically circular or rectangular and generally measure activity with only one or a few photobeams. Siegel [101] is credited with using the first photocell cage to monitor activity. This device consisted of a rectangular box with a single photobeam oriented along the long axis. In 1953, Dews [23] employed a similar device to record the effects of pharmacological agents on the motor activity of mice (see also [108, 109, 129]). Numerous experiments have been conducted by Iversen and her colleagues on the effects of various treatments on the activity of rats in rectangular cages with parallel photobeams horizontally directed along the long axis (e.g. [18, 19, 54]). Rectangular chambers have also been employed in which one or two photobeams bisect the chamber across the short axis (e.g., [25, 60, 69]) and in which photobeams intersect at right angles (e.g., [41, 89, 127]).

Several simple circular photocell chambers have been used with a variety of photobeam arrangements (e.g., [29,133]). One chamber measures approximately 60 cm in diameter and is transected by two sets of three beams that intersect at right angles. Separate counts are available for the two banks of photobeams. The device has been used extensively to assess the effects of several chemical and nonchemical treatments on motor activity (e.g., [14, 38, 40, 110]),

although lately it has been supplanted by more sophisticated photocell chambers (see below).

There is a recurring concern over the importance of photocell placement [60,133]. Watzman *et al.* [133], for example, compared the effects of chlorpromazine on activity of mice tested with two different photobeam arrangements and tested either individually or in groups of five. When three parallel beams transected the chamber, more interruptions were recorded under control conditions from each of the two peripheral beams than from the center one. Also, the number of center beam interruptions was less than that obtained when the beam was oriented at a right angle with a second beam. Chlorpromazine decreased activity in a dose-dependent fashion, and this decrease depended on both the group size and on the particular photobeam arrangement. At low doses of chlorpromazine a significant dose-response was found for the crisscross photocell arrangement but not for the parallel arrangement. Therefore, with a given chamber configuration, the photocell arrangement may affect the sensitivity of a measurement technique.

In the pieces of apparatus described above, the orientation of the photobeams is along the horizontal plane. An alternative approach is to direct the photobeams downward to the sensors. One of the earliest devices that used this arrangement was described by Schnitzer and Ross [95] in which light from a single overhead source impinged on photocells located below a translucent plastic floor. Although the device has the advantage of using only one light source, thereby eliminating problems with photocell alignment, a possible limitation is that with too dense a concentration of photocells, beam interruptions could conceivably be produced by non-locomotor activities such as head turning, tail swishes, and defecation [55]. This limitation highlights a continuing concern with the use of photocell chambers: whereas too few photobeams would allow significant amounts of locomotor activity to go undetected, too many photobeams increase the likelihood that non-locomotor activities will contribute to the measurement.

Almost without exception, most simple photocell devices permit recording of horizontally-directed locomotor activity (ambulation) and exclude measurement of vertically-directed activity (rearing). In addition, very little information is collected regarding the spatial distribution of locomotor activity. There is at least one commercial photocell device, however, which can be used to measure both rearing and the spatial distribution of activity. The Electronic Motility Meter manufactured by Motron Products consists of a rectangular platform with a translucent plastic floor with 40 photosensors situated underneath. Infrared light is provided by a single overhead source. With an appropriate data-collection device, information can be collected on the spatial distribution of locomotor activity by recording and storing individual photobeam interruptions. In addition, the device has an adjustable array of photobeams and sensors for detecting rearing. The Motron device has been used for investigating the effects of drugs and other variables on locomotor activity (e.g. [1, 2, 4, 16, 33, 35, 36, 65, 77, 128, 130, 131]). Very few of these studies, however, have collected rearing data, and to date there has been no published investigation of treatment effects on the spatial distribution of locomotor activity. Although the device has many advantages over the other simple photocell test chambers currently in use, the same concerns regarding density of photocells that were discussed above apply here. Additionally, widespread use of the Motron chamber has been hampered by its high cost. At present, however, there has been at least one attempt to develop a similar but much less expensive prototype [80].

Adaptation to these simple test environments occurs rapidly, with animals showing initial high levels of activity that decrease to asymptotically low levels after several (e.g. 10–60) minutes. Downward trends in activity levels are also evident with repeated testing. Since asymptotic levels are characteristically low, simple test environments are well suited for detection of chemically induced increases in locomotor activity and/or retardation of the within-session habituation of activity.

b. Complex test environments. We consider a photocell chamber to be complex if it contains more than a single boundary. For example, a variety of otherwise simple photocell test chambers include an obstruction in the center area. One device is doughnut-shaped with the light source located in the center of the annulus and an array of six photosensors spaced equidistantly on the outer periphery. The device was first described by Wright *et al.* [136] and was manufactured as the Woodard Actophotometer. It has been used to investigate the effects of drugs and biochemical lesions of the central nervous system on motor activity (e.g. [14, 21, 62, 125, 137]). A related device was used by Kršiak *et al.* [57] in which light impinged on two photocells that intersected at right angles at the center of a square testing area. Access to the center of the chamber was precluded by a square translucent column, which was included to prevent excess activity counts by an animal simultaneously interrupting both photobeams at or near their point of intersection.

It is important to note that devices such as that used by Kršiak *et al.* [57] and Wright *et al.* [136] may have unique operating characteristics as a result of this central obstruction. It is frequently demonstrated, for example, that the locomotor activity of rodents tends to concentrate at the periphery of the test area (i.e., "wall-seeking" behavior or thigmotaxis which has been described by Barnett [4]; see also [59]). Since devices with central obstructions provide two boundaries for wall-seeking to find expression, it is likely that the relationship between locomotor activity and an independent variable differs from that found with devices that permit access to the center of the test area.

Support for this notion comes from an experiment by Stewart [113] on the effect of environmental complexity on locomotor activity in control and in scopolamine-treated rats. Although direct observation and not a photocell device was used to measure activity, the results illustrate how a complex boundary can modify behavior. Figure 1 shows the within-session time course of locomotor activity for control rats and rats treated with scopolamine (0.25 mg/kg). In a simple open field, scopolamine-treated rats had a higher level of activity than controls. However, when the complexity of the environment was increased by adding walls which divided the field into either two (C1) or four (C2) compartments, the scopolamine-treated animals were less active than controls. This difference in the drug response was due to both an increase in the rate of habituation of drug-treated animals and to a decrease in the rate of habituation of the controls. The rate of habituation, therefore, was a function of the complexity of the environment as well as the drug.

Norton *et al.* [71] have described a more complex photocell chamber with two continuous alleys that connect to a small central area and that form a figure eight when placed on its side. Two additional blind alleys extend from the central area and may provide stimuli such as water or a nest box. Locomotor activity in the figure-eight alleys is detected by

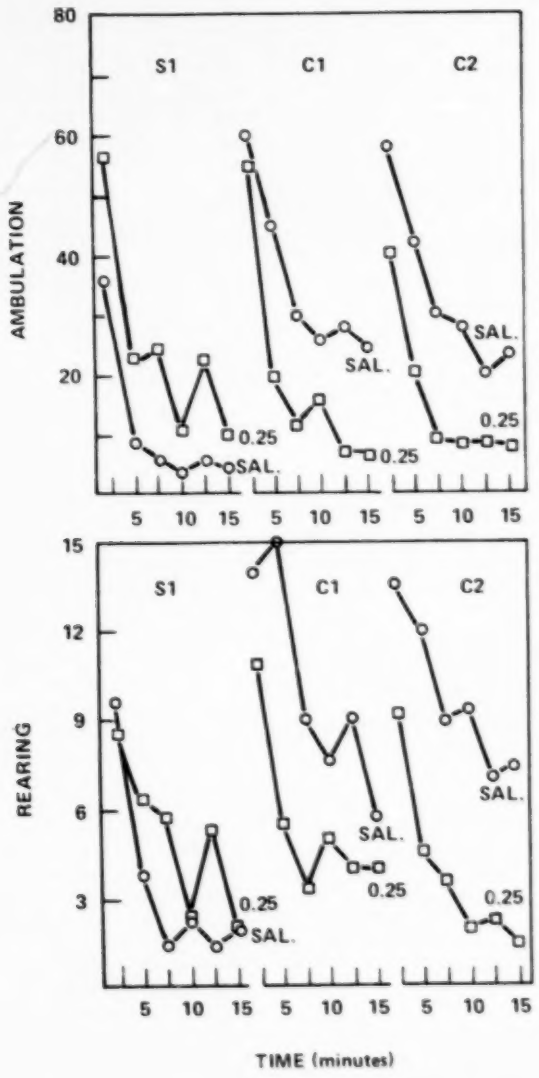


FIG. 1. Mean squares entered (ambulation) and rearing responses in saline- and scopolamine-treated (0.25 mg/kg) rats tested in three 36×36 in. environments differing in complexity (S1, simple; C1, one insert; C2, two interlocking inserts, in the field) during 2.5 min intervals of the 15 min test session. (Redrawn from: Stewart, Neurosci. Lett. **1**: 121–125, 1975.)

six pairs of photobeam and sensor and an additional beam and sensor detects excursions into each of the blind alleys. The device has been used extensively by Norton and her colleagues in studies of the effects on locomotor activity of time-of-day and social variables, as well as exposure to psychoactive drugs and environmental pollutants [71, 72, 85, 86, 87, 88].

In light of the above discussion of environmental complexity, it is interesting to compare the rate of habituation in this test chamber with habituation in the open field. Whereas Stewart [113] reported that habituation occurred within 10 min in a simple open field, this process extends over hours in the maze. These two test environments may, therefore, be expected to differ in their sensitivity to detect chemically induced alteration in the habituation process.

Ljungberg and Ungerstedt [61] have recently described a device which purports to measure several key aspects of motor activity. The outer boundary of the chamber is square with a square obstruction in the center. Horizontally oriented photobeams and sensors detect ambulation and vertically oriented beams and sensors record entries into the corners of the chamber. The floor is replete with holes below which horizontally oriented beams and sensors detect head (and other types of) entries. Finally, a microphone is used to detect gnawing behavior. Preliminary data suggest that the device is capable of recording several behavioral effects produced by drugs that alter transmission in dopamine-containing neurons. Although the device can be used to measure the spatial distribution of activity, it does not record rearing behavior. At this time, it remains to be seen whether conclusions regarding the effects of chemicals on locomotor activity obtained with this device are in any way more precise than those obtained with simpler devices.

2. Mechnical Measurements

The motor activity recorded with these devices involves a vertical or horizontal displacement of the chamber in response to the animal's movement. The displacement is transduced to a digital electronic signal which is counted. As with any type of mechanical measurement device, care must be taken to insure that activity counts are not confounded by momentum. Displacement of the chamber will depend in part on the age and weight of the animal. Additionally, it should be noted that mechanical devices may provide proprioceptive feedback that is positively correlated with motion.

a. Stabilimeters. Stabilimeters are so named because movements of the animal cause the chamber to be displaced from its resting position. Displacement may be in either the horizontal or vertical plane.

1. Jiggle cages. Richter [90] described a triangular activity measurement device for rats. Movements displaced the chamber vertically and this was transduced pneumatically and recorded on a revolving smoked-drum kymograph. This type of jiggle cage does not allow separate determination of rearing and ambulation, nor does it as a rule allow determination of an animal's location within the chamber. Depending on the sensitivity, non-locomotor activities may or may not be recorded.

Another type of jiggle cage, the Williamson jiggle cage, confines the animal in a very restrictive environment (approximately 15 cm in all directions). The transduction of displacements is characteristically complex [123], which makes calibration and, consequently, standardization difficult. Moreover, the device routinely detects fine-grained non-locomotor activities (e.g., tremor and face-washing) in rodents. The device has had only limited employment in the past two decades (e.g. [34, 120, 123, 124]).

Davis and Ellison [20] have described a device in which the floor of the test chamber rests on ball bearings, and movement causes the floor to displace laterally. Transduction is accomplished by closing a circuit between a metal plumb bob, that is normally centered (but not touching) within a hole in the floor just outside the chamber, and a thin film of metal that is wrapped around the rim of the hole. This

device suffers from the same limitations (e.g., carry-over effects and dependence of displacement on body weight) described above for most of the mechanical measurement devices. In addition, since the device records only lateral displacements it has an undefined relationship to the more common devices which record vertical displacements.

2. Tilt cage. Perhaps the most widely used of the tilt cages was originally described by Bousfield and Mote [16] and subsequently modified by Campbell *et al.* [12]. A wire-mesh rectangular cage rests on a central fulcrum that runs across the chamber's width. Ambulation from one side to the other causes a slight vertical displacement of the cage which activates a microswitch. This type of tilt cage has been used extensively to characterize the effects of development, deprivation, temperature, time of day, drugs, and biochemical, electrolytic and mechanical lesions of the central nervous system (e. g. [8, 11, 27, 28, 30, 48, 49, 66, 67]). The most positive feature of this device is its simplicity and, consequently, its ease of construction and standardization. Moreover, in contrast to the jiggle cage, it is insensitive to relatively minor non-locomotor activities such as grooming and tremor. A significant limitation, however, is that some locomotor activity may go unrecorded if the animal does not cross from one side the fulcrum to the other. Also, the device does not record rearing, and provides only a crude estimate of the spatial locus of activity. Finally, although momentum (carry-over) effects are negligible, the device does provide proprioceptive stimuli as positive feedback for ambulation.

Circular tilt cages have also been described. Eayrs [26], for example, described a doughnut-shaped wire-mesh chamber that was balanced on a central pivot. Movement about the cage was detected by making and breaking electrical connections between pairs of brass contacts that were placed at 90° intervals underneath the chamber. Interestingly, in a counterbalanced crossover design, Eayrs [26] found no correlation between daily levels of activity of female rats measured in the circular tilt cage and those measured in a running wheel. Campbell [8] has also described a circular tilt cage, but it has not received widespread use.

3. Force platforms. Force platforms are those in which ambulatory movements cause very small displacements of the floor of the chamber. Movements are either digitized to increment counters or in other cases an analog signal is the output. Segal and Mandell [100], for example, described a chamber in which horizontal locomotor activity was recorded as crossovers on a floor that was electronically divided into quadrants. Rearing was recorded by metal touch plates located on the walls approximately 12 cm above the floor (rearing that did not include wall contact went unrecorded). That the device was relatively insensitive to small non-locomotor activities was shown in the following way. Large doses of *d*-amphetamine had a triphasic effect on activity: an initial increase in locomotor activity was followed by a period in which the rats exhibited stereotyped sequences of sniffing, grooming and gnawing. During this phase of amphetamine intoxication, ambulation and rearing were virtually absent and no activity counts were recorded. After approximately 1.5–2 hr, stereotyped behavior subsided and was accompanied by a return of locomotor activity. Although the device has many positive features, it has not been extensively used [97–100].

A particularly elegant force platform has recently been described by Denenberg and co-workers [22]. A large square test arena is supported on four corner-mounted electromechanical force transducers that provide analog outputs which are proportional to their respective supportive forces. With this device, and an appropriate data-acquisition system, it is possible to record all horizontally directed movements of the animal, however small. It is also possible to measure the spatial distribution of ambulation and, conceivably, the exact path the animal takes in moving about the chamber. Measurements have been shown to correlate well with ambulation measured by an observer [37]; it has an advantage over the open field of recording ambulation that does not result in a grid crossover [22]. It does not, however, permit registration of rearing. To date, there are no published data on the effects of chemical or non-chemical treatments on ambulation with this device and, consequently, its utility for toxicity testing remains to be determined.

b. Wheels. Running wheels are ordinarily designed so that the wheel is mounted on a horizontal axle and the animal's ambulation within the wheel causes it to rotate on its axle. The direction of rotation of the wheel may be unidirectional or bidirectional, and transduction may be accomplished in any number of ways [94, 106, 107]. Prevention of rotation with a braking device is not uncommon [78,94]. Running wheels have been used in animal behavior for over three-quarters of a century and were originally described by Stewart [112] in 1898. Skinner [106] provides an excellent description of the construction of a running wheel and the variables that influence the measurement of ambulation.

It should be obvious that ambulation recorded in running wheels involves considerable neuromuscular coordination. Also, there is considerable stimulation in the form of proprioceptive feedback, that correlates positively with the level of ambulation. The specialized nature of this activity is perhaps best reflected in the time-course for establishing stable levels of activity. In rats, activity in the running wheel typically increases with repeated testing [15, 26, 31, 91] even though the within-session trend is downward. Once asymptotic levels are reached, however, they may be very stable for long periods [15,26], although fluctuations about the mean are apparent, for example, with estrus or time of day. Large individual differences in baseline levels may be apparent [47]. Unless special precautions are taken, momentum may influence activity counts.

Running wheels have been used to study the effects of food deprivation, water deprivation, estrus, ambient temperature and time of day, lesions of the central nervous system, and a wide array of drugs on locomotor activity (e.g. [8, 32, 45–47, 51, 52, 78, 94, 96, 118, 122, 123, 134, 138]).

3. Field Detectors

Many devices have been introduced recently that record the disturbances that an organism creates in moving about a prearranged field within the test cage. Both ultrasonic and capacitive fields have been employed and each has the advantage of being stationary and, therefore, providing no feedback stimulation for activity. Measurements of activity are also unconfounded by momentum effects. The principle limitations of these techniques, however, have to do with both the degree to which locomotor activity counts may be inflated with non-locomotor activity data and the inability to adequately calibrate these devices.

a. Ultrasonic field detectors. These devices deliver an acoustic signal to the test chamber that creates a three-dimensional pattern of standing waves (e.g. [74,75]). Movements of an organism produce changes in the pattern of energy which are ordinarily transmitted to a microphone, di-

gitized and counted. The degree of pattern interference is correlated with the speed and extent of body movement. Typically, the sensitivity of the devices can be varied over a wide range, as can the size of the test chamber. Problems arise, however, over uncertainties regarding the uniformity of the propagated field. Operating characteristics may change with fluctuations in temperature and humidity, or the deposition of fecal material. Standardization of one or more instruments is extremely tedious. Artifacts may arise through electrical interference with the signal that is sent to the counter; for this reason, coaxial cable is required. Despite the limitations described above, these types of field detectors may be of use especially when a measure of general motor activity is desired.

b. Capacitance-sensing devices. These devices utilize a tuned oscillator circuit. In the simplest case, an adjustable oscillator supplies high-frequency current to an input coil which creates a field around the test chamber. Movement within the chamber produces momentary changes in the voltage that is induced in the output coil. This signal is then amplified and an output pulse is counted. Devices of this type (e.g., Animex and Varimex) have been used extensively to evaluate drug effects (e.g. [5, 50, 52, 63, 68, 81, 104, 116, 119]). Svensson and Thieme [121] have described the uses and limitations of the Animex for recording motor activity in control and drug-treated mice. Although commercially available models are being continually refined, many of the same uses and limitations that characterize ultrasonic field sensing devices are also applicable.

4. Touch Plates

The devices in this category are included because they do not fit handily into any of the above categories. Although these devices all measure motor activity by recording contacts of the animal with sections of the chamber floor, they differ in the means used to detect these contacts.

a. Proximity counter. The floor of this device is comprised of a rectangular checkerboard arrangement of copper-clad phenolic plates that are separated by insulating material. A low-voltage oscillating current is passed between alternate plates and is adjusted so that ambulation from a ground plate to an active plate produces changes in the frequency of the oscillating current. The magnitude of this change in current is a function of the animal's capacitance, and it is this change that is typically amplified, transduced and counted. Although the principle of proximity counters is not new [139], there are very few investigations which have used them. The most notable instances are the experiments carried out by Silbergeld and her colleagues on the effect of postnatal lead exposure on the motor activity of mice (e.g. [102]). Silbergeld's device records primarily large-scale ambulatory activity; rearing would not be recorded unless it occurred concomitantly with a crossover from one to another floor plate. Although the results of these experiments have stimulated much research, no apparent attempt has been made to critically evaluate the relationship between the activity that is measured in a proximity counter and that measured in one of the more conventional devices.

b. Touch plates. These devices represent modifications of the chamber originally described by Kissel [56] and by Eayrs [26]. The basic chamber consists of a small circular alley that creates a somewhat restrictive and complex test environment for monitoring motor activity. Because of its restrictive interior, it is likely that the age and size of the rodent will determine whether ambulation is largely unidirectional or bidirectional. The original chambers were suspended on a central pivot, and in some instances delicately balanced with counter weights [26]. Movement about the chamber produced displacements that operated microswitches which in turn were used to increment counters. Subsequent modifications replaced the pivot arrangement with small floor plates that were spaced equidistantly about the cage and which rested on microswitches [83]. Although this type of chamber detects ambulation and is relatively unaffected by the occurrence of non-locomotor activities, it has no means for recording rearing. More importantly, however, its complex configuration, together with its restrictive interior, raise the possibility that the effect of a treatment may be much more complex than that determined in a larger chamber which has no central obstruction. A salient example of the complex nature of the locomotor activity recorded by this device is the dose-response curve for *d*-amphetamine [116]. In rats, increasing doses of *d*-amphetamine produce progressively greater increases in locomotor activity until a dosage of 2–4 mg/kg is reached. Further dosage increases up to about 12 mg/kg produce either no greater increase or a decrease in locomotor activity. In most instances, however, dosages of 12 mg/kg and beyond produce further increases in activity. At these heroic dosages, it is likely that a measure of ambulation reflects more the occurrence of the repetitive behavioral sequences that are produced by *d*-amphetamine than an effect of the drug on ambulation *per se*. The device has been used in several studies on the effects of psychoactive and biogenic amine-depleting drugs (e.g. [82, 83, 114–116]).

CROSS-COMPARISONS OF MOTOR-ACTIVITY-MEASUREMENT DEVICES

A limited number of studies has compared two or more measures of motor activity either in nontreated animals or in animals subjected to different types of treatments.

Tapp *et al.* [123] compared several different measures of motor activity in rats. Their results showed a lack of correlation between the various activity measures shown in Table 6. When, however, two measures were taken within the same apparatus (i.e., measures of activity within the circular field), a significant correlation was found. Otherwise, there was generally no correlation between relative levels of activity in the different test environments.

Tapp [124] has also investigated the effect of food deprivation on several measures of activity. Food deprivation did not affect activity in a Williamson jiggle cage, and decreased activity in both a simple photocell cage and a complex doughnut-shaped mechanical device (circular field). There are additional data that support the conclusion that the effects of food deprivation are apparatus-dependent. Strong [117], for example, studied the effect of food deprivation on stabilimeter activity under two conditions of measurement sensitivity. Food deprivation did not affect activity when measured in a microswitch-operated stabilimeter and decreased it when measured in a more sensitive stabilimeter device. On the other hand, Weasner *et al.* [134] obtained increases in photocell-cage activity and activity in a running wheel with food deprivation. Campbell [8] also obtained increases in activity in a running wheel and in a stabilimeter during food deprivation. The latter two studies both obtained greater increases in activity in the wheels than with the other types of measurement device. Finger [32] has also shown

TABLE 6

MATRIX OF INTERCORRELATIONS BETWEEN ACTIVITY MEASURES

Test Number	Test	1	2	3	4	5
1	Williamson Cages		−0.03	0.11	0.18	0.19
2	Photocell Cages			−0.02	−0.01	0.11
3	Activity Wheel				0.15	0.19
4	Circular Field (alternations)					0.90*
5	Circular Field (total counts)					

*$p<0.01$ Adapted from Tapp, *et al.* (Psychol. Rep. **23:** 1047–1050, 1968)

that substantially greater changes in activity occur during the estrus cycle of rats when measured in wheels than in a simple photocell device.

Animals treated with various drugs or toxicants have also been shown to respond differently when tested in different activity devices. Reiter *et al.* [86] reported changes in activity of male rats exposed to the pesticide Kepone which were apparatus-dependent. Following three weeks of treatment, rats showed a dose-related increase in locomotor activity in a figure-eight maze but a dose-related decrease in activity in an open field (Fig. 2).

The data of Kršiak *et al.* [57] illustrate further the limitations of a single measure of motor activity (Fig. 3). They examined motor activity in rats following administration of either *d*-amphetamine (dexamphetamine) or amobarbital (amylobarbitone). Animals were placed in a complex test environment (described earlier) and activity was determined simultaneously by recording photocell interruptions and by direct observation of walking, rearing and grooming. In saline-treated animals, the combined frequency of walking and rearing closely agreed with activity levels determined by photocell interruptions. In these animals, photocell counts were significantly correlated with both walking and rearing (r=0.68 and 0.79, respectively). However, with increasing doses of *d*-amphetamine, photocell activity counts exceeded the observationed activity. Following 1.0 mg/kg of *d*-amphetamine, walking (r=0.82) but not rearing (r=0.11) was correlated with photocell counts. On the other hand, following administration of amobarbital, there was a close agreement between photocell interruptions and observational scoring of walking and rearing.

There also appear to be discrepancies between the effects of drugs on activity measured in photocell cages and those measured in capacitance-sensing devices. Maj *et al.* [63] found that the activity of rats was about equally reduced following reserpine or α-methyl-*para*-tyrosine in both the Animex chamber and a simple photocell chamber. A large dose of *l*-dopa substantially blocked the decrease produced by reserpine and by α-methyl-*para*-tyrosine in activity measured in the Animex but not that measured in the photocell cage. Amantadine produced a dose-related blockade of the effect of reserpine on activity in the Animex chamber whereas the largest dose produced only a slight blockade of the effect in the photocell chamber. Similarly, Ljungberg [60] found that whereas a small dose of apomorphine decreased activity in both a simple photocell cage and an Animex chamber, a large dose had no effect on activity in the former

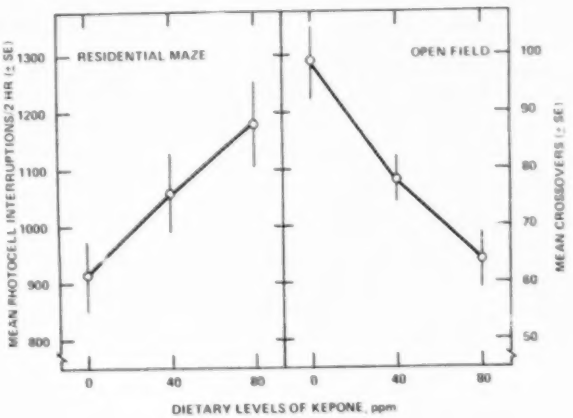


FIG. 2. Effects of dietary kepone exposure (3 weeks) on two measures of locomotor activity in the rat. Kepone exposure produced a dose-related increase in locomotor activity in a figure-eight maze but a decreased activity in an open field. (From: Reiter *et al.*, Toxic. appl. Pharmac. **41:** 143, 1977.)

device but increased it in the latter device. The effects of several other drug treatments showed no correlation between activity measurements in the two types of devices.

Experimentally induced brain damage is another manipulation which is reported to produce apparatus-dependent changes in activity. Capobianco and Hamilton [13], for example, employed several activity measures with rats sustaining lesions of the fornix, diagonal band, and the medial forebrain bundle. Lesions of the medial forebrain bundle and diagonal band reliably increased activity in a revolving wheel whereas lesions of the fornix had a much smaller effect. Lesions of the medial forebrain bundle and the diagonal band, on the other hand, either had no effect or decreased activity in a stabilimeter whereas fornix lesions substantially increased activity. Measures of both open-field ambulation and rearing were unaffected by these lesions. This experiment suffers, however, from one possible source of experimental error which was recognized by the authors: stabilimeter testing always preceded open-field testing. It is possible that an "order effect" of testing could account for the lack of a treatment effect on activity in the open field. If, for example, lesions of the diagonal band altered the animal's reactiv-

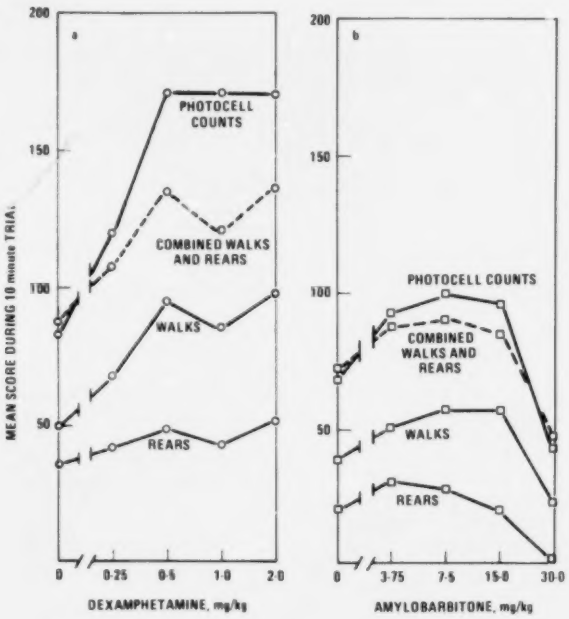


FIG. 3. Ten groups of 8 rats were injected subcutaneously either with saline or a dose of a drug 35 min before a 10 min trial in the activity cage. After dexamphetamine, marked discrepancies occurred when the results with photocells were compared with observation (Fig. 3a), but agreement was close after amylobarbitone (Fig. 3b). (Adapted from: Kršiak *et al.*, Psychopharmacology **17**: 258–274, 1970.)

ity to a novel environment, then a "carry over" effect from stabilimeter to open field would preclude detection of an effect in the latter.

Table 7 represents data obtained in adult male rats tested on successive days in a figure-eight (Residential) maze and in an open field. The order of testing was counterbalanced so that half the animals were tested first in each apparatus. Order of testing had a significant effect on activity in the open field when animals had prior exposure to the maze but the converse was not true. This potential for a carry-over effect in open-field testing has obvious implications for experiments using multiple test systems.

TABLE 7

EFFECT OF ORDER OF TESTING ON RESIDENTIAL MAZE ACTIVITY AND OPEN FIELD ACTIVITY IN ADULT RATS

	Open Field First		Residential Maze First	
Open Field (5-minutes) $t = 4.378$ 43df $p<0.005$	67.5 ± 4.8	1st	40.3 ± 3.8	2nd
Residential Maze (5-minutes) $t = 1.33$ 43df NS	76.3 ± 8	2nd	61.3 ± 8	1st
Residential Maze (120-minutes) $t = 1.116$ 43df NS	1099 ± 67	2nd	950 ± 82	1st

CONCLUSIONS

A. Direct observations are indispensible in preliminary toxicity testing since many overt neurotoxic symptoms (i.e., tremor or ataxia) are readily detected by direct observation. The problem with this approach is that the data are not amenable to quantitative analysis.

B. Quantitative characterization of a chemical effect on motor activity can be carried out using any number of non-automated and automated techniques. Quantitative observational techniques may be used to detect subtle changes, but they require personnel commitments, not found with automated techniques, which ultimately limit the number of animals which can be tested.

C. Many automated techniques are available for recording motor activity. The particular components of motor activity which are measured depend on the particular technique chosen. Numerous chemical and nonchemical treatments have been shown to selectively affect various components of motor activity. It is imperative, therefore, to know which components of activity a particular device is likely to detect.

D. Relationships between devices will be understood only when they are compared by measuring one or a few components of motor activity. We recommend that different devices be compared on the basis of their ability to measure locomotor activity since this represents a major component of motor activity and since most devices are designed to detect this movement. This restricted focus on locomotor activity is likely to uncover certain fundamental relationships and/or differences between the devices. We recognize, however, one possible shortcoming of this approach: since treatments may selectively affect various components of motor activity, too great a restriction on the variables to be measured may decrease sensitivity of the measure.

E. A basic requirement of activity measurements is that test methods be standardized at least within a given laboratory and that experimental details be extensively reported.

F. It is premature to conclude which of the many available activity measuring techniques is *the* most appropriate for behavioral toxicity testing. Appreciation of the relative sensitivity of the different devices will come when extensive data have been collected under standardized laboratory conditions. Future studies should, therefore, compare different measures of motor activity following exposure to neurotoxic substances.

REFERENCES

1. Ahlenius, S., N.-E. Anden and J. Engel. Restoration of locomotor activity in mice by low *l*-dopa doses after suppression by α-methyl-tyrosine but not by reserpine. *Brain Res.* **62:** 189–199, 1973.
2. Andén, N.-E., U. Strömbom and T. H. Svensson. Dopamine and noradrenaline receptor stimulation: Reversal of reserpine-induced suppression of motor activity. *Psychopharmacology* **29:** 289–298, 1973.
3. Archer, J. Tests for emotionality in rats and mice: A review. *Anim. Behav.* **21:** 205–235, 1973.
4. Barnett, S. H. *The Rat: A Study in Behavior.* Chicago: Aldine Publishing Co., 1963, pp. 31–32.
5. Benkert, O. Measurement of hyperactivity in rats in a dose-response-curve after intrahypothalamic norepinephrine injection. *Life Sci.* **8:** 943–948, 1969.
6. Bousfield, W. A. and F. A. Mote. The construction of a tilting activity cage. *J. exp. Psychol.* **32:** 450–451, 1943.
7. Brase, D. A., H. H. Loh and E. L. Way. Comparison of the effects of morphine on locomotor activity, analgesia and primary and protracted physical dependence in six mouse strains. *J. Pharmac. exp. Ther.* **201:** 368–374, 1977.
8. Campbell, B. A. Theory and research on the effects of water deprivation on random activity in the rat. In: *Thirst. Proceedings from the 1st International Symposium on Thirst in the Regulation of Body Water.* Oxford: Pergamon Press, 1964, pp. 317–334.
9. Campbell, B. A. and G. A. Cicala. Studies of water deprivation in rats as a function of age. *J. comp. physiol. Psychol.* **55:** 763–768, 1962.
10. Campbell, B. A. and P. D. Mabry. The role of catecholamines in behavioral arousal during ontogenesis. *Psychopharmacology* **31:** 253–264, 1973.
11. Campbell, B. A., L. D. Lytle and H. C. Fibiger. Ontogeny of adrenergic arousal and cholinergic inhibitory mechanisms in the rat. *Science* **166:** 637–638, 1969.
12. Campbell, B. A., R. Teghtsoonian and R. A. Williams. Activity, weight loss and survival time of food deprived rats as a function of age. *J. comp. physiol. Psychol.* **54:** 216–219, 1961.
13. Capobianco, S. and L. W. Hamilton. Effects of interruption of limbic system pathways on different measures of activity. *Physiol. Behav.* **17:** 65–72, 1976.
14. Carey, R. J. and A. P. Salim. Changes in *d*-amphetamine reactivity resulting from septal forebrain injury. *Physiol. Behav.* **5:** 133–136, 1970.
15. Cornish, E. R. and N. Mrosovsky. Activity during food deprivation and satiation of six species of rodent. *Anim. Behav.* **13:** 242–248, 1965.
16. Costa, E., A. Groppetti and M. K. Naimzada. Effects of (+)-amphetamine on the turnover rate of brain catecholamines and motor activity. *Br. J. Pharmac.* **44:** 742–751, 1972.
17. Costa, E., K. M. Naimzada and A. Revuelta. Phenmetrazine, aminorex and (±)-*p*-chloroamphetamine, their effects on motor activity and turnover rate of brain catecholamines. *Br. J. Pharmac.* **43:** 570–579, 1972.
18. Creese, I. and S. D. Iversen. Blockage of amphetamine-induced motor stimulation and stereotypy in the adult rat following neonatal treatment with 6-hydroxydopamine. *Brain Res.* **55:** 369–382, 1973.
19. Creese, I. and S. D. Iversen. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res.* **83:** 419–436, 1975.
20. Davis, J. D. and G. D. Ellison. A general purpose activity recorder with variable sensitivity. *J. exp. Analysis Behav.* **7:** 117–118, 1964.
21. Davis, W. M., M. Babbini, S. F. Pong, W. T. King and C. L. White. Motility of mice after amphetamine: Effects of strain, aggregation and illumination. *Pharmac. Biochem. Behav.* **2:** 803–809, 1974.
22. Denenberg, V. H., J. Gartner and M. Myers. Absolute measurement of open field activity in mice. *Physiol. Behav.* **15:** 505–509, 1975.
23. Dews, P. B. The measurement of the influence of drugs on voluntary activity in mice. *Br. J. Pharmac. Chemother.* **8:** 46–48, 1953.
24. Draper, W. A. A behavioral study of the home cage activity of the white rat. *Behaviour* **28:** 280–293, 1967.
25. Dyer, R. S., D. A. Weldon and A. H. Thoumaian. Task-specific effects of *d*-amphetamine and blindness of BALB/cj mice. *Physiol. Psychol.* **4:** 175–179, 1976.
26. Eayrs, J. T. Spontaneous activity in the rat. *Br. J. Anim. Behav.* **2:** 25–30, 1954.
27. Erinoff, L., R. C. MacPhail, A. Heller and L. S. Seiden. Age-dependent effects of 6-hydroxydopamine on locomotor activity in the rat. *Brain Res.* **64:** 195–205, 1979.
28. Fibiger, H. C. and B. A. Campbell. The effect of *para*-chlorophenylalanine on spontaneous locomotor activity in the rat. *Neuropharmacology* **10:** 25–32, 1971.
29. Fibiger, H. C., C. Trimbach and B. A. Campbell. Enhanced stimulant properties of (+)-amphetamine after chronic reserpine treatment in the rat: Mediation by hypophagia and weight loss. *Neuropharmacology* **11:** 57–67, 1972.
30. Fibiger, H. C., L. D. Lytle and B. A. Campbell. Cholinergic modulation of adrenergic arousal in the developing rat. *J. comp. physiol. Psychol.* **72:** 384–389, 1970.
31. Finger, F. W. Measuring behavioral activity. In: *Methods in Psychobiology*, Vol. 2, edited by R. D. Myers. New York: Academic Press, 1972, pp. 1–19.
32. Finger, F. W. Estrus activity as a function of measuring device. *J. comp. physiol. Psychol.* **55:** 100–102, 1961.
33. Foldes, A. and E. Costa. Relationship of brain monoamine and locomotor activity in rats. *Biochem. Pharmac.* **24:** 1617–1621, 1975.
34. Freeman, J. J. and F. Sulser. Iprindole-amphetamine interactions in the rat: The role of aromatic hydroxylation of amphetamine in its mode of action. *J. Pharmac. exp. Ther.* **183:** 307–315, 1972.
35. Fuentes, J. A. and N. H. Neff. Selective monoamine oxidase inhibitor drugs as aids in evaluating the role of Type A and B enzymes. *Neuropharmacology* **14:** 819–825, 1975.
36. Fuentes, J. A., M. A. Oleshansky and N. H. Neff. Comparison of the apparent antidepressant activity of (−)- and (+)-tranylcypromine in an animal model. *Biochem. Pharmac.* **25:** 801–804, 1976.
37. Gartner, J., M. Myers, V. H. Denenberg and S. Bhat. A center-of-pressure force platform for open field activity tests. *Trans. Second New Engl. Bioengineer. Conf.*, 449–457, 1975.
38. Glick, S. D. and S. Millory. Rate-dependent effects of *d*-amphetamine on locomotor activity in mice: Possible relationship to paradoxical amphetamine sedation in minimal brain dysfunction. *Eur. J. Pharmac.* **24:** 266–268, 1973.
39. Goldstein, A., L. Aronow and S. M. Kalman. *Principles of Drug Action: The Basis of Pharmacology*, 2nd edition. New York: John Wiley and Sons, 1974, p. 735.
40. Gordon, J. H. and M. K. Schellenberger. Regional catecholamine content in the rat brain: Sex differences and correlation with motor activity. *Neuropharmacology* **13:** 129–137, 1974.
41. Grant, M. Cholinergic influences on habituation of exploratory activity in mice. *J. comp. physiol. Psychol.* **86:** 853–857, 1974.
42. Hollister, A. S., G. R. Breese and B. R. Cooper. Comparison of tyrosine hydroxylase and dopamine-β-hydroxylase inhibition with the effects of various 6-hydroxydopamine treatments on *d*-amphetamine-induced motor activity. *Psychopharmacology* **36:** 1–16, 1974.
43. Hollister, A. S., G. R. Breese, C. M. Kuhn, B. R. Cooper and S. M. Schanberg. An inhibitory role for brain serotonin-containing systems in the locomotor effects of *d*-amphetamine. *J. Pharmac. exp. Ther.* **198:** 12–22, 1976.

44. *Human Health and the Environment–Some Research Needs*. U.S. Department of Health, Education and Welfare, Public Health Service/National Institutes of Health. Washington, D.C.: U.S. Government Printing Office, 1977.
45. Irwin, S. Comprehensive observational assessment: Ia. A systematic, quantitative procedure for assessing the behavioral and physiologic state of the mouse. *Psychopharmacology* **13:** 222–257, 1968.
46. Irwin, S. The action of drugs on psychomotor activity. *Rev. Can. Biol.* **20:** 239–250, 1961.
47. Irwin, S., M. Slabok and G. Thomas. Individual differences: I. Correlation between control locomotor activity and sensitivity to stimulant and depressant drugs. *J. Pharmac. exp. Ther.* **123:** 206–211, 1958.
48. Jacobs, B. L., W. D. Wise and K. M. Taylor. Differential behavioral and neurochemical effects following lesions of the dorsal or median raphe nuclei in rats. *Brain Res.* **79:** 353–361, 1974.
49. Jacobs, B. L., C. Trimbach, E. E. Eubanks and M. Trulson. Hippocampal mediation of raphe lesion and PCPA-induced hyperactivity in the rat. *Brain Res.* **94:** 253–261, 1975.
50. Jenner, P. and C. D. Marsden. The influence of piribedil (ET495) on components of locomotor activity. *Eur. J. Pharmac.* **33:** 211–215, 1975.
51. Karczmar, A. G., C. L. Scudder and D. L. Richardson. Interdisciplinary approach to the study of behavior in related mice types. In: *Neurosciences Research, Vol. 5, Chemical Approaches to Brain Function*, edited by I. Kopin and S. Ehrenpries. New York: Academic Press, 1973, pp. 159–244.
52. Kavanau, J. L. and D. H. Brant. Wheel-running preferences of *Peromyscus*. *Nature* **208:** 597–598, 1965.
53. Kellogg, C. and P. Lundborg. Ontogenic variations in responses to *l*-dopa and monoamine receptor-stimulating agents. *Psychopharmacology* **23:** 187–200, 1972.
54. Kelly, P. H., P. W. Seviour and S. D. Iversen. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.* **94:** 507–522, 1975.
55. Kinnard, W. J. and N. Watzman. Techniques utilized in the evaluation of psychotropic drugs on animal activity. *J. Pharmac. Sci.* **55:** 995–1012, 1966.
56. Kissel, J. W. Nutating annular cage for measuring motor activity. *Science* **134:** 1224–1225, 1963.
57. Kršiak, M., H. Steinberg and I. P. Stolerman. Uses and limitations of photocell activity cages for assessing effects of drugs. *Psychopharmacology* **17:** 258–274, 1970.
58. Kuschinsky, K. Are cholinergic mechanisms involved in morphine effects on motility? *Naunyn-Schmiedeberg's Arch. Pharmac.* **281:** 167–173, 1974.
59. Làt, J. The spontaneous exploratory reaction as a tool for psychopharmacological studies. A contribution towards a theory of contradictory results in psychopharmacology. In: *Pharmacology of Conditioning, Learning and Retention*, edited by M. Mikhel'son, V. G. Longo and Z. Votava. New York: Pergamon Press, 1965, pp. 47–66.
60. Ljungberg, T. Reliability of two activity boxes commonly used to assess drug-induced behavioral changes. *Pharmac. Biochem. Behav.* **8:** 191–195, 1978.
61. Ljungberg, T. and U. Ungerstedt. A method for simultaneous recording of eight behavioral parameters related to monoamine neurotransmission. *Pharmac. Biochem. Behav.* **8:** 483–489, 1978.
62. Maickel, R. P., R. M. Levine and J. E. Zabik. Differential effects of *d*- and *l*-amphetamine on spontaneous motor activity in mice. *Res. commun. chem. pathol. Pharmac.* **8:** 711–714, 1974.
63. Maj, J., B. Durek and W. Palider. Differences in locomotor activity of mice as measured by an Animex and photoresistor actometer. *J. Pharmac. Pharmac.* **23:** 979–981, 1971.
64. McCall, R. B., M. L. Lester and C. M. Corter. Caretaker effects in rats. *Devl. Psychol.* **1:** 771, 1969.
65. Modigh, K. Central and peripheral effects of 5-hydroxytryptophan on motor activity in mice. *Psychopharmacology* **23:** 48–54, 1972.
66. Moorcroft, W. H. Ontogeny of forebrain inhibition of behavioral arousal in the rat. *Brain Res.* **35:** 513–522, 1971.
67. Moorcroft, W. H., L. D. Lytle and B. A. Campbell. Ontogeny of starvation-induced behavioral arousal in the rat. *J. comp. physiol. Psychol.* **75:** 59–67, 1971.
68. Mukherjee, B. P., P. T. Bailey and S. N. Pradhan. Correlation of lithium effects on motor activity with its brain concentrations in rats. *Neuropharmacology* **16:** 241–244, 1977.
69. Nagy, Z. M. and M. Ritter. Ontogeny of behavioral arousal in the mouse: Effects of prior testing upon age of peak activity. *Bull. Psychon. Soc.* **7:** 285–288, 1976.
70. Norton, S. Amphetamine as a model for hyperactivity in the rat. *Physiol. Behav.* **11:** 181–186, 1973.
71. Norton, S., B. Culver and P. Mullenix. Measurement of the effects of drugs on activity of permanent groups of rats. *Psychopharm. Commun.* **1:** 131–138, 1975.
72. Norton, S., P. Mullenix and B. Culver. Comparison of the structure of hyperactive behavior in rats after brain damage from x-irradiation, carbon monoxide and pallidal lesions. *Brain Res.* **116:** 49–67, 1976.
73. Norton, S. and W. Servos. Pattern recognition of rat behavior using a laboratory computer. 5th Int. Congress of Pharmacology, July 1972.
74. Peacock, L. J. and M. Williams. An ultrasonic device for recording activity. *Am. J. Psychol.* **75:** 648–652, 1962.
75. Peacock, L. J., M. H. Hodge and R. K. Thomas. Ultrasonic measurements and automatic analysis of general activity in the rat. *J. comp. physiol. Psychol.* **62:** 284–288, 1966.
76. Pirch, J. H. and R. H. Rech. Behavioral recovery in rats during chronic reserpine treatment. *Psychopharmacology* **12:** 115–122, 1968.
77. Post, R. M. and H. Rose. Increasing effects of repetitive cocaine administration in the rat. *Nature* **260:** 731–732, 1976.
78. Premack, D. Towards empirical behavioral laws: I. Positive reinforcement. *Psychol. Rev.* **66:** 219–233, 1959.
79. *Principles for Evaluating Chemicals in the Environment*. National Academy of Sciences, Washington, D.C., 1975.
80. Rafales, L. S., R. L. Bornschein, I. A. Michaelson, R. K. Loch and G. F. Barker. Drug induced activity in lead-exposed mice. *Pharmac. Biochem. Behav.* **10:** 95–104, 1979.
81. Rastogi, R. B. and R. L. Singhal. Lithium: Modification of behavioral activity and brain biogenic amines in developing hyperthyroid rats. *J. Pharmac. exp. Ther.* **201:** 92–102, 1977.
82. Rech, R. H. Antagonism of reserpine behavioral depression by *d*-amphetamine. *J. Pharmac. exp. Ther.* **146:** 369–376, 1964.
83. Rech, R. H., L. A. Carr and K. E. Moore. Behavioral effects of α-methyltyrosine after prior depletion of brain catecholamines. *J. Pharmac. exp. Ther.* **160:** 326–335, 1968.
84. Reed, J. D. Spontaneous activity of animals: A review of the literature since 1929. *Psychol. Bull.* **44:** 393–412, 1947.
85. Reiter, L. W., G. E. Anderson, J. W. Laskey and D. F. Cahill. Developmental and behavioral changes in the rat during chronic exposure to lead. *Envir. Hlth Perspect.* **12:** 119–123, 1975.
86. Reiter, L. W., K. Kidd, G. Ledbetter, L. Gray and N. Chernoff. Comparative behavioral toxicology of mirex and Kepone in the rat. *Toxic. appl. Pharmac.* **41:** 143, 1977.
87. Reiter, L. W. Behavioral toxicology: Effects of early postnatal exposure to neurotoxins on development of locomotor activity in the rat. *J. occup. Med.* **19:** 201–204, 1977.
88. Reiter, L. W. Use of activity measures in behavioral toxicology. *Envir. Hlth Perspect.* **26:** 9–20, 1978.
89. Remington, G. and H. Anisman. Genetic and ontogenetic variations in locomotor activity following treatment with scopolamine or *d*-amphetamine. *Devl. Psychobiol.* **9:** 579–585, 1976.
90. Richter, C. P. Animal behavior and internal drives. *Q. Rev. Biol.* **2:** 307–343, 1927.
91. Robbins, T. W. A critique of the methods available for the measurement of spontaneous motor activity. In: *Handbook of Psychopharmacology*, Vol. 7, edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. New York: Plenum Press, 1977, pp. 37–82.

92. Rushton, R., H. Steinberg and C. Tinson. Effects of single experience on subsequent reaction to drugs. *Br. J. Pharmac.* **20:** 99–105, 1963.
93. Rushton, R., H. Steinberg and M. Tomkiewicz. Equivalence and persistence of the effects of psychoactive drugs and past experience. *Nature* **220:** 885–889, 1968.
94. Schaeffer, R. W. A new device for programming contingencies between drinking, running and level pressing. *J. exp. Analysis Behav.* **9:** 3–24, 1963.
95. Schnitzer, S. B. and S. Ross. Effects of physiological saline injections on locomotor activity in C57BL/6 mice. *Psychol. Rep.* **6:** 351–354, 1960.
96. Searle, L. V. and C. W. Brown. The effect of subcutaneous injections of benzedrine sulfate on the activity of white rats. *J. exp. Psychol.* **22:** 480–490, 1938.
97. Segal, D. S. Behavioral characterization of *d*- and *l*-amphetamine: Neurochemical implications. *Science* **190:** 475–477, 1975.
98. Segal, D. S. Behavioral and neurochemical correlates of repeated *d*-amphetamine administration. In: *Neurobiological Mechanisms of Adaptation and Behavior*, edited by A. J. Mandel. New York: Raven Press, 1975, pp. 247–262.
99. Segal, D. S. Differential effects of *para*-chlorophenylalanine on amphetamine-induced locomotion and stereotypy. *Brain Res.* **116:** 267–276, 1976.
100. Segal, D. S. and A. J. Mandell. Long-term administration of *d*-amphetamine: Progressive augmentation of motor activity and stereotypy. *Pharmac. Biochem. Behav.* **2:** 249–255, 1974.
101. Siegel, P. S. A simple electronic device for the measurement of gross bodily activity of small animals. *J. Psychol.* **21:** 227–236, 1946.
102. Silbergeld, E. K. and A. M. Goldberg. A lead-induced behavioral disorder. *Life Sci.* **13:** 1275–1283, 1973.
103. Silverman, A. P. and H. Williams. Behaviour of rats exposed to trichloroethylene vapour. *Br. J. Ind. Med.* **32:** 308–315, 1975.
104. Simpson, L. L. A study of the interaction between amphetamine and food deprivation. *Psychopharmacology* **38:** 279–286, 1974.
105. Skinner, B. F. *The Behavior of Organisms: An Experimental Analysis*. New York: Appleton-Century-Crofts, Inc., 1938, pp. 362–363.
106. Skinner, B. F. The measurement of spontaneous activity. *J. gen. Psychol.* **9:** 3–24, 1933.
107. Skinner, B. F. and W. H. Morse. Concurrent activity under fixed-interval reinforcement. *J. comp. physiol. Psychol.* **50:** 279–281, 1957.
108. Smith, C. B. Enhancement by reserpine and α-methyl dopa of the effects of *d*-amphetamine upon locomotor activity of mice. *J. Pharmac. exp. Ther.* **142:** 343–350, 1963.
109. Smith, C. B. and P. B. Dews. Antagonism of locomotor suppressant effects of reserpine in mice. *Psychopharmacology* **3:** 55–59, 1962.
110. Sobotka, T. J. and M. P. Cook. Postnatal lead acetate exposure in rats: Possible relationship to minimal brain dysfunction. *Am. J. Ment. Defic.* **79:** 5–9, 1974.
111. Steinberg, H., R. Rushton and C. Tinson. Modification of the effects of an amphetamine-barbiturate mixture by the past experience of rats. *Nature* **192:** 533–535, 1961.
112. Stewart, C. C. Variations in daily activity produced by alcohol and by changes in barometric pressure and diet, with a description of recording methods. *Am. J. Physiol.* **1:** 40–56, 1898.
113. Stewart, W. J. Environmental complexity does affect scopolamine induced changes in activity. *Neurosci. Let.* **1:** 121–125, 1975.
114. Stolk, J. M. and R. H. Rech. Enhanced stimulant effects of *d*-amphetamine on the spontaneous motor activity of rats treated with reserpine. *J. Pharmac. exp. Ther.* **158:** 140–149, 1967.
115. Stolk, J. M. and R. H. Rech. Enhanced stimulant effects of *d*-amphetamine in rats treated chronically with reserpine. *J. Pharmac. exp. Ther.* **163:** 75–83, 1968.
116. Stolk, J. M. and R. H. Rech. Antagonism of *d*-amphetamine by alpha-methyl-*l*-tyrosine: Behavioral evidence for the participation of catecholamine stores and synthesis in the amphetamine stimulant response. *Neuropharmacology* **9:** 249–263, 1970.
117. Strong, P. N. Activity in the white rat as a function of apparatus and hunger. *J. comp. physiol. Psychol.* **50:** 596–600, 1957.
118. Strong, P. N. and W. J. Jackson. Effects of hippocampal lesions in rats on three measures of activity. *J. comp. physiol. Psychol.* **70:** 60–65, 1970.
119. Su, M.-Q. and G. T. Okita. Behavioral effects on the progeny of mice treated with methylmercury. *Toxic. appl. Pharmac.* **38:** 195–205, 1976.
120. Sulser, F., M. L. Owens, N. R. Norvich and J. V. Dingell. The relative role of storage and synthesis of brain norepinephrine in the psychomotor stimulation evoked by amphetamine or by desipramine and tetrabenazine. *Psychopharmacology* **12:** 322–332, 1968.
121. Svensson, T. H. and G. Thieme. An investigation of a new instrument to measure motor activity of small animals. *Psychopharmacology* **14:** 157–163, 1969.
122. Tainter, M. L. Effects of certain analeptic drugs on spontaneous running activity in the white rat. *J. comp. Psychol.* **36:** 143–155, 1943.
123. Tapp, J. T., R. S. Zimmerman and P. S. D'Encarnacao. Intercorrelational analysis of some common measures of rat activity. *Psychol. Rep.* **23:** 1047–1050, 1968.
124. Tapp, J. T. Activity, reactivity and the behavior-directing properties of stimuli. In: *Reinforcement and Behavior*, edited by J. T. Tapp. New York: Academic Press, 1969, pp. 146–177.
125. Thornburg, J. E. and K. E. Moore. A comparison of effects of apomorphine and ET495 on locomotor activity and circling behavior in mice. *Neuropharmacology* **13:** 189–197, 1974.
126. Toman, J. E. P. and G. M. Everett. In: *Psychopharmacology*, edited by H. Pennes. New York: Hoeber-Harper, 1958, p. 248.
127. van Rossum, J. M. and F. Simons. Locomotor activity and anorexogenic action. *Psychopharmacology* **14:** 248–254, 1969.
128. Vasko, M. R., M. P. Lutz and E. F. Domino. Structure-activity relations of some indolealkylamines in comparison to phenethylamines on motor activity and acquisition of avoidance behavior. *Psychopharmacology* **36:** 49–58, 1974.
129. Villareal, J. E., M. Guzman and C. B. Smith. A comparison of the effects of *d*-amphetamine and morphine upon the locomotor activity of mice treated with drugs which alter brain catecholamine content. *J. Pharmac. exp. Ther.* **187:** 1–7, 1973.
130. Waldeck, B. Modification of caffeine-induced locomotor stimulation by a cholinergic mechanism. *J. Neural Transm.* **35:** 197–205, 1974.
131. Waldeck, B. On the interaction between caffeine and barbiturates with respect to locomotor activity and brain catecholamines. *Acta pharmac. toxic.* **36:** 172–180, 1975.
132. Walsh, R. N. and R. A. Cummins. The open-field test: A critical review. *Psychol. Bull.* **83:** 482–504, 1976.
133. Watzman, N., H. Barry, III, W. J. Kinnard, Jr. and J. P. Buckley. Comparison of different photobeam arrangements for measuring spontaneous activity in mice. *J. Pharmaceut. Sci.* **55:** 907–909, 1966.
134. Weasner, M. H., F. W. Finger and L. S. Reid. Activity changes under food deprivation as a function of recording device. *J. comp. physiol. Psychol.* **53:** 470–474, 1960.
135. Weissman, A., B. K. Koe and S. S. Tenen. Antiamphetamine effects following inhibition of tyrosine hydroxylase. *J. Pharmac. exp. Ther.* **151:** 339–352, 1966.
136. Wright, L. S., H. J. Horn, Jr. and G. Woodard. Activity patterns in mice tested singly and in groups as a drug screening tool. *Fedn. Proc.* **21:** 420, 1962.
137. Zabik, J. E., R. M. Levine and R. P. Maickel. Drug interactions with brain biogenic amines and the effects of amphetamine isomers on locomotor activity. *Pharmac. Biochem. Behav.* **8:** 429–435, 1978.
138. Zieve, L. Effect of benzedrine on activity. *Psychol. Rec.* **1:** 343–346, 1937.
139. Zucker, M. H. *Electronic Circuits for the Behavioral and Biomedical Sciences*. San Francisco: W. H. Freeman, 1969, Chapter 6.